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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/068,635	ANDERSON ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4&5&6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an application filed on 2/5/02. There are thirty claims pending and thirty under consideration. Claims 1-3 are compound claims. Claim 4 and 9-14 is a composition claim. Claims 5-8 and 15-30 are use claims. This is the first action on the merits. The application concerns some 1,6-dihydropurine compounds, compositions, and uses thereof.

2. There is a discrepancy between the formula of claim 1 and working example 9 pictured in Figure 1. Claim 1 is drawn to 1,6-dihydropurine compounds with a single bond between N-1 and C-6 with a hydrogen atom on N-1. The figure as drawn in claim 1 does not violate the chemical rules of valence. Working Example 9 has a double bond between N-1 and C-1 and does not possess a hydrogen atom on N-1. Working example 9 is also in compliance with the rules of chemical valence. The Examiner will make two sets of rejections, one drawn to the dihydropurine compounds, as presently claimed, and a second contingent set to the fully aromatic purine compounds.

Title

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: replacing –Novel Compounds— by "2-Amino-9H-purin-9-yl".

Abstract

4. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Specification

5. If Applicants are intending to claim the fully aromatic purine compounds, then the disclosure is objected to because of the following informalities: the two figures on page 6 and the figure on page 7 have a single bond between N-1 and C-6 with a hydrogen atom on N-1. Appropriate correction is required. Applicants must show clear support in the specification for any changes made to avoid introducing new matter. While there is support for the single species of working example 9, Applicants must show support in the specification for any generic fully aromatic purine formula. Applicants are reminded of MPEP §2163 "[w]hile there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. An amendment to correct an obvious error does not constitute new matter where one

skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)." The Examiner sees no obvious error to the generic formulas described above.

6. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). The testing procedure outlined in the second complete paragraph on page 23 requires the material from Larder, which was not supplied, to understand completely what testing was done. This issue is developed more completely in the enablement rejection to HIV treatment made below.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1 and 3 offer "ether group" as a possible group R^1 or R^2. This is indefinite for three reasons. Hawley (The Condensed Chemical Dictonary) defines ether as, "a class of organic compounds *** giving the generic formula ROR". Applicants say in line 14, page 10, "R^1 is preferably a C_1 to C_{20} hydrocarbon or substituted hydrocarbon and is more preferably an alkyl group". Firstly, since an ether is a molecule it cannot be the monovalent radical, which R^1 is required to be. Seconly, the open terms "preferably" do not limit R^1 to be either a hydrocaron or an alkyl group. Hawley (The Condensed Chemical Dictonary) offers cellulose as an example in his defintaion. Could R^1 be a radical derived from cellulose? Thirdly, if R^1 is a hydrocarbon, by what may it be susbtituted?

The Examiner suggests replacing the term –ether group-- by "C_1 to C_{20} alkyl" relying upon the fact that an alkyl group is a subtype of hydrocarbon, so that new matter is not introduced.

8. If Applicants are intending to claim the fully aromatic purine compounds, then claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1, 3, 5, 7, 9, 15, and 23, the formula is drawn with a single bond between N-1 and C-6 with a hydrogen atom on N-1. Applicants must show clear support in the specification for any changes made to the claims to avoid introducing new matter. While there is support for the single species of working example 9, Applicants must show support in the specification for any generic fully aromatic purine formula. Applicants are reminded of MPEP §2163 "[w]hile there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)." The Examiner sees no obvious error to the generic formulas described above.

9. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The word "combination" has been misspelled.

10. Claims 12, 18, and 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "TIBO-derivative" is indefinite. A derivative is the result of a reaction upon an organic molecule. Since we do not know the reagents or the conditions of these reactions, there is no way of determining the structures of the claimed "derivatives". The word "TIBO-derivative" is, in essence, a product by process claim. Yet Applicants have not described the intended processes sufficiently that we may understand the structures of the compounds they claim.

The Examiner suggests deleting the word.

11. Claims 12, 13, 18, 19, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. What are the drugs "GW 420", "867X", and "Iopinavir"? Search of the NIH Anti-HIV/OI chemical compound database at http://apps1.niaid.nih.gov/struct_search/an/AN_search.htm# fails to reveal any hits for these compounds.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention. Applicants do not teach how to make the 1,6-dihydropurine compounds with a single bond between N-1 and C-6 with a hydrogen atom on N-1. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Preparing Applicants' claimed compounds will require selective reduction of the taught purine compounds, a moderate degree of experimentation. b) Synthetic direction is found in the second paragraph in page 15. There is no direction concerning this required purine reduction in the specification. The

displacement reaction, replacing the chlorine atom of compound 8 with a claimed substituent X, will only occur on the fully aromatic purine compounds. This displacement reaction is taught in the last two lines on page 22 and the first paragraph on page 23 but is not applicable to the synthesis of the claimed compounds. c) There is no working example of synthesis of a compound of formula given in claim 1. d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art is that search of the CASREACT reaction file reveals that no such reduction method is known that would selectively reduce only the N-1 to C-6 double bond of any 2-amino purine. The reduction would be particularly difficult to perform in the presence of the double bond in Applicants' dihydrofuran ring. f) The artisan using Applicants invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the thousands of compounds of formula of claim 1.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to

make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

13. Claims 5-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating infections by Human T Cell Leukemia Virus (HTLV), does not reasonably provide enablement for treating HIV infections. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. There are two separate issues Firstly, it is unclear if compound 9 was tested against the HIV virus or against the HTLV virus and if there is any correlation between HTLV and HIV.

The factors to be considered in making an enablement rejection have been summarized above. a) Determining if any particular claimed compound would treat HIV infection would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a moderate degree of experimentation. b) The direction concerning treating HIV is found in the first paragraph on page 19, which merely states Applicants' intention to do so.

Applicants describe formulations in the passage spanning paragraph 2, page 16 through paragraph 1, page 17. Doses are taught in the passage spanning paragraph 3, page 17 through paragraph 2, page 18. A 2,500-fold range of doses was proposed. There is an *in vitro* assay described in the second paragraph, page 23, with a single compound. The MT-2 cell line is described as "infected with Leukemia Virus (HTLV) and shows morphological and cytotoxic effects upon infection with HIV. Was HIV used in this assay or only HTLV? Does the use of the present tense "shows" indicate this was a prophetic experiment for HIV? Applicants do not assert and it is not understood by the Examiner that treatment of HTLV is related to treatment HIV or other retroviral diseases. c) There is no working example of treatment of any disease in man or animals. There are no working examples of any formulated drug. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in HIV treatment is found in the background of the invention section in pages 2-4.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable

factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1. Thus, the scope of claims is very broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

14. Claims 5-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating infections by Human T Cell Leukemia Virus (HTLV) with compound 9, does not reasonably provide enablement for treating any infections with the compounds of claim 1. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. These claimed dihydro purine compounds have never been made, let alone tested in any biological assay.

15. Claims 7, 8, 10, and 23-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Human T Cell

Leukemia Virus (HTLV), does not reasonably provide enablement for preventing infection by any virus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. No HIV vaccine has ever been developed. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of HIV. In addition, it is presumed that "reducing the likelihood that an individual will contract HIV" would require a method of identifying those individuals who will develop HIV before they become infected. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

The factors to be considered in making an enablement rejection have been summarized above. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before infection occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) Paragraph 4, page 14 and paragraph 2, page 19 lists Applicants' intend to prevent HIV infection. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical infective medicine and are therefore physiological in

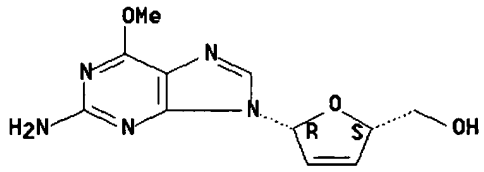
nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally HIV will infect before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in infectious diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of HIV. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent HIV infection. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing HIV therapy and on the multitude of compounds embraced by claim 1. Thus, undue experimentation will be required to practice Applicants invention.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

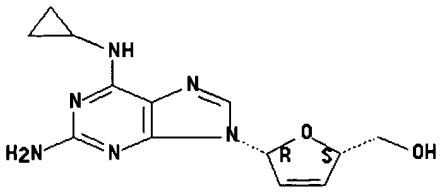
If Applicants are intending to claim the fully aromatic purine compounds, then claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Robins (Journal of Organic Chemistry). The compound shown below almost fits formula of claim 1 with $R^1 = R^2$ = hydrogen and X = methoxyl. It has Registry Number 214900-45-5 and is found in the figure in Scheme 1, page 7376 of the reference. It is compound 9b. Synthesis is taught in the paragraph spanning pages 7381-7382.



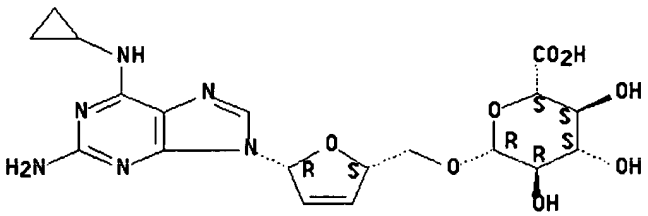
Allowable Subject Matter

17. If Applicants are intending to claim the fully aromatic purine compounds, then their compounds are novel over Katagiri (Journal of Organic Chemistry, cited by Applicants). Chemical Abstracts cites the compound shown below as located in this reference. The compound shown below almost fits formula of claim 1 with $R^1 = R^2$ = hydrogen and X = aminocyclopropyl. It has Registry Number 188525-24-8.

However the compound 1b (called 1592U89) found in the figure in column 1, page 1580 of the reference is a cyclopentene not a dihydrofuran. Thus, the CA citation must be an error.



18. If Applicants are intending to claim the fully aromatic purine compounds, then their compounds are novel over McDowell (Antimicrobial Agents and Chemotherapy). Chemical Abstracts cites the compound shown below as located in this reference. The compound shown below almost fits formula of claim 1 with R^1 = the ether group D-glucopyranuronosyl, R^2 = hydrogen and X = aminocyclopropyl. It has Registry Number 256423-90-2. However the compound called 361W94 and described in column 2, page 2855 of the reference is a metabolite of Abacavir (1592U89) and must be a cyclopentene not a dihydrofuran. Thus, the CA citation must be an error.



Conclusion

19. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
June 17, 2003